

What is Claimed is:

1. A substantially monodispersed mixture of conjugates, each conjugate comprising a drug coupled to an oligomer that comprises a polyalkylene glycol moiety.
2. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 2, 3 or 4 polyalkylene glycol subunits.
3. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 5 or 6 polyalkylene glycol subunits.
4. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.
5. The mixture according to Claim 4, wherein the oligomer is covalently coupled to the drug.
6. The mixture according to Claim 4, wherein the oligomer further comprises a lipophilic moiety.
7. The mixture according to Claim 4, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.
8. The mixture according to Claim 7, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.
9. The mixture according to Claim 8, wherein the oligomer further comprises a lipophilic moiety.
10. The mixture according to Claim 7, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

11. The mixture according to Claim 10, wherein the polypropylene glycol moiety is uniform.

12. The mixture according to Claim 11, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

13. The mixture according to Claim 1, wherein at least 96, 97, 98 or 99 percent of the conjugates in the mixture have the same molecular weight.

14. The mixture according to Claim 1, wherein the mixture is a monodispersed mixture.

15. The mixture according to Claim 1, wherein the mixture is a substantially purely monodispersed mixture.

16. The mixture according to Claim 1, wherein at least 96, 97, 98 or 99 percent of the conjugates in the mixture have the same molecular weight and the same molecular structure.

17. The mixture according to Claim 1, wherein the mixture is a purely monodispersed mixture.

18. The mixture according to Claim 17, wherein the oligomer is covalently coupled to the drug.

19. The mixture according to Claim 17, wherein the oligomer further comprises a lipophilic moiety.

20. The mixture according to Claim 17, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

21. The mixture according to Claim 20, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

22. The mixture according to Claim 21, wherein the oligomer further comprises a lipophilic moiety.

23. The mixture according to Claim 20, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

24. The mixture according to Claim 23, wherein the polypropylene glycol moiety is uniform.

25. The mixture according to Claim 24, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

26. The mixture according to Claim 1, wherein the mixture has an *in vivo* activity that is greater than the *in vivo* activity of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the mixture.

27. The mixture according to Claim 1, wherein the mixture has an *in vitro* activity that is greater than the *in vitro* activity of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the mixture.

28. The mixture according to Claim 1, wherein the mixture has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the mixture.

29. The mixture according to Claim 1, wherein the mixture has an inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of drug-oligomer conjugates having the same number average molecular weight as the mixture.

30. The mixture according to Claim 1, wherein the drug is a polypeptide.

31. The mixture according to Claim 30, wherein the polypeptide is selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin peptides, dynorphin peptides, endorphin peptides, endothelin peptides, ETa receptor
10 antagonist peptides, ETb receptor antagonist peptides, enkephalin peptides, fibronectin peptides, galanin peptides, gastrin peptides, glucagon peptides, Gn-RH associated peptides, growth factor peptides, growth hormone peptides, GTP-binding protein fragment peptides, guanylin peptides, inhibin peptides, insulin peptides, interleukin peptides, laminin peptides, leptin peptides, leucokinin peptides, luteinizing hormone-releasing hormone peptides, mastoparan peptides, mast cell degranulating peptides, melanocyte stimulating hormone peptides, morphiceptin peptides, motilin peptides, neuro-peptides, neuropeptide Y peptides, neurotropic factor peptides, orexin peptides, opioid peptides, oxytocin peptides, PACAP peptides, pancreastatin peptides, pancreatic polypeptides, parathyroid hormone peptides,
15 parathyroid hormone-related peptides, peptide T peptides, prolactin-releasing peptides, peptide YY peptides, renin substrate peptides, secretin peptides, somatostatin peptides, substance P peptides, tachykinin peptides, thyrotropin-releasing hormone peptides, toxin peptides, vasoactive intestinal peptides, vasopressin peptides, and virus related peptides.
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32. The mixture according to Claim 31, wherein the oligomer is covalently coupled to a nucleophilic residue of the polypeptide.

33. The mixture according to Claim 31, wherein the oligomer further comprises a lipophilic moiety.

34. The mixture according to Claim 31, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

35. The mixture according to Claim 34, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

36. The mixture according to Claim 35, wherein the oligomer further comprises a lipophilic moiety.

37. The mixture according to Claim 34, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

38. The mixture according to Claim 37, wherein the polypropylene glycol moiety is uniform.

39. The mixture according to Claim 38, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

40. The mixture according to Claim 1, wherein the oligomer is covalently coupled to the drug.

41. The mixture according to Claim 1, wherein the oligomer further comprises a lipophilic moiety.

42. The mixture according to Claim 1, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

43. The mixture according to Claim 42, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

44. The mixture according to Claim 43, wherein the oligomer further comprises a lipophilic moiety.

45. The mixture according to Claim 42, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

46. The mixture according to Claim 45, wherein the polypropylene glycol moiety is uniform.

47. The mixture according to Claim 46, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

48. The mixture according to Claim 1, wherein each conjugate comprises a plurality of oligomers.

49. The mixture according to Claim 48, wherein each oligomer in the plurality of oligomers is the same.

50. The mixture according to Claim 1, wherein the oligomer comprises a first polyalkylene glycol moiety covalently coupled to the drug by a non-hydrolyzable bond and a second polyalkylene glycol moiety covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond.

51. The mixture according to Claim 1, wherein the oligomer further comprises a lipophilic moiety covalently coupled to the second polyethylene glycol moiety.

52. The mixture according to Claim 1, wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

53. A pharmaceutical composition comprising:

the mixture according to Claim 1; and
a pharmaceutically acceptable carrier.

54. A mixture of conjugates each comprising a drug coupled to an oligomer that comprises a polyalkylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

55. The mixture according to Claim 54, wherein the standard deviation of the molecular weight distribution is less than about 14 Daltons.

56. The mixture according to Claim 54, wherein the standard deviation of the molecular weight distribution is less than about 11 Daltons.

57. The mixture according to Claim 54, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

58. The mixture according to Claim 57, wherein the lower alkyl polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

59. The mixture according to Claim 57, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

60. The mixture according to Claim 59, wherein the oligomer further comprises a lipophilic moiety.

61. The mixture according to Claim 57, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

62. The mixture according to Claim 61, wherein the polypropylene glycol moiety is uniform.

63. The mixture according to Claim 62, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

64. The mixture according to Claim 54, wherein the drug is a polypeptide selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin
10 peptides, dynorphin peptides, endorphin peptides, endothelin peptides, ETa receptor antagonist peptides, ETb receptor antagonist peptides, enkephalin peptides, fibronectin peptides, galanin peptides, gastrin peptides, glucagon peptides, Gn-RH associated peptides, growth factor peptides, growth hormone peptides, GTP-binding protein fragment peptides, guanylin peptides, inhibin peptides, insulin peptides, interleukin peptides, laminin peptides, leptin peptides, leucokinin peptides, luteinizing hormone-releasing hormone peptides,
15 mastoparan peptides, mast cell degranulating peptides, melanocyte stimulating hormone peptides, morphiceptin peptides, motilin peptides, neuro-peptides, neuropeptide Y peptides, neurotropic factor peptides, orexin peptides, opioid peptides, oxytocin peptides, PACAP peptides, pancreastatin peptides, pancreatic polypeptides, parathyroid hormone peptides, parathyroid hormone-related peptides, peptide T peptides, prolactin-releasing peptides,
20 peptide YY peptides, renin substrate peptides, secretin peptides, somatostatin peptides, substance P peptides, tachykinin peptides, thyrotropin-releasing hormone peptides, toxin peptides, vasoactive intestinal peptides, vasopressin peptides, and virus related peptides.

65. A mixture of conjugates each comprising a drug coupled to a polymer comprising a polyalkylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 \sum_{i=1}^n N_i - \left(\sum_{i=1}^n N_i M_i \right)^2}$$

5 wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

66. The mixture according to Claim 65, wherein the dispersity coefficient is greater than 100,000.

67. The mixture according to Claim 65, wherein the dispersity coefficient is greater than 500,000.

68. The mixture according to Claim 65, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

69. The mixture according to Claim 68, wherein the lower alkyl polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

70. The mixture according to Claim 68, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

71. The mixture according to Claim 70, wherein the oligomer further comprises a lipophilic moiety.

72. The mixture according to Claim 68, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

73. The mixture according to Claim 72, wherein the polypropylene glycol moiety is uniform.

74. The mixture according to Claim 73, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

75. The mixture according to Claim 65, wherein the drug is a polypeptide selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin
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76. A mixture of conjugates in which each conjugate:
comprises a drug coupled to an oligomer; and
has the same number of polyalkylene glycol subunits.

77. The mixture according to Claim 76, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene glycol moiety.

78. The mixture according to Claim 77, wherein the lower alkyl polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

79. The mixture according to Claim 77, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

80. The mixture according to Claim 79, wherein the oligomer further comprises a lipophilic moiety.

81. The mixture according to Claim 77, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

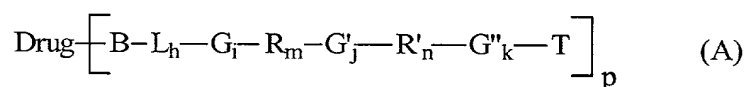
82. The mixture according to Claim 81, wherein the polypropylene glycol moiety is uniform.

83. The mixture according to Claim 82, wherein the oligomer is devoid of a lipophilic moiety, and wherein the conjugate is amphiphilically balanced such that it is aqueously soluble and able to penetrate biological membranes.

84. The mixture according to Claim 76, wherein the drug is a polypeptide selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin

10 peptides, dynorphin peptides, endorphin peptides, endothelin peptides, ETa receptor antagonist peptides, ETb receptor antagonist peptides, enkephalin peptides, fibronectin peptides, galanin peptides, gastrin peptides, glucagon peptides, Gn-RH associated peptides, growth factor peptides, growth hormone peptides, GTP-binding protein fragment peptides, guanylin peptides, inhibin peptides, insulin peptides, interleukin peptides, laminin peptides, 15 leptin peptides, leucokinin peptides, luteinizing hormone-releasing hormone peptides, mastoparan peptides, mast cell degranulating peptides, melanocyte stimulating hormone peptides, morphiceptin peptides, motilin peptides, neuro-peptides, neuropeptide Y peptides, neurotropic factor peptides, orexin peptides, opioid peptides, oxytocin peptides, PACAP peptides, pancreastatin peptides, pancreatic polypeptides, parathyroid hormone peptides, 20 parathyroid hormone-related peptides, peptide T peptides, prolactin-releasing peptides, peptide YY peptides, renin substrate peptides, secretin peptides, somatostatin peptides, substance P peptides, tachykinin peptides, thyrotropin-releasing hormone peptides, toxin peptides, vasoactive intestinal peptides, vasopressin peptides, and virus related peptides.

85. A mixture of conjugates in which each conjugate has the same molecular weight and has the formula:



wherein:

- 5 B is a bonding moiety;
 L is a linker moiety;
 G, G' and G'' are individually selected spacer moieties;
 R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;
 10 T is a terminating moiety;
 h, i, j, k, m and n are individually 0 or 1, with the proviso that when R is the polyalkylene glycol moiety; m is 1, and when R' is the polyalkylene glycol moiety, n is 1; and
 p is an integer from 1 to the number of nucleophilic residues on the drug.

86. The mixture according to Claim 85, wherein the polyalkylene glycol moiety is a lower alkyl polyalkylene moiety.

87. The mixture according to Claim 86, wherein the lower alkyl polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

88. The mixture according to Claim 86, wherein the lower alkyl polyalkylene glycol moiety is a polyethylene glycol moiety.

89. The mixture according to Claim 88, wherein:

R is the polyethylene glycol moiety;

R' is a lipophilic moiety;

n and m are 1; and

i, j and k are 0.

90. The mixture according to Claim 88, wherein:

R is a lipophilic moiety;

R' is the polyethylene glycol moiety;

n and m are 1; and

i, j and k are each 0.

91. The mixture according to Claim 86, wherein the lower alkyl polyalkylene glycol moiety is a polypropylene glycol moiety.

92. The mixture according to Claim 91, wherein the polypropylene glycol moiety is uniform.

93. The mixture according to Claim 92, wherein:

R is the polypropylene glycol moiety;

m is 1;

i, j, k and n are each 0; and

each conjugate in the mixture is amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

94. The mixture according to Claim 85, wherein the drug is a polypeptide selected from the group consisting of adrenocorticotrophic hormone peptides, adrenomedullin peptides, allatostatin peptides, amylin peptides, amyloid beta-protein fragment peptides, angiotensin peptides, antibiotic peptides, antigenic polypeptides, anti-microbial peptides, apoptosis
 5 related peptides, atrial natriuretic peptides, bag cell peptides, bombesin peptides, bone GLA peptides, bradykinin peptides, brain natriuretic peptides, C-peptides, C-type natriuretic peptides, calcitonin peptides, calcitonin gene related peptides, CART peptides, casomorphin peptides, chemotactic peptides, cholecystokinin peptides, colony-stimulating factor peptides, corticotropin releasing factor peptides, cortistatin peptides, cytokine peptides, dermorphin
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95. A process for synthesizing a substantially monodispersed mixture of conjugates each conjugate comprising a drug coupled to an oligomer that comprises a polyethylene glycol moiety, said process comprising:

5 reacting a substantially monodispersed mixture comprising compounds having the structure of Formula I:



wherein R^1 is H or a lipophilic moiety; m is from 1 to 25; and X^+ is a positive ion,

with a substantially monodispersed mixture comprising compounds having the structure of
Formula II:



wherein R^2 is H or a lipophilic moiety; and n is from 1 to 25,
under conditions sufficient to provide a substantially monodispersed mixture comprising
polymers having the structure of Formula III:



activating the substantially monodispersed mixture comprising polymers of Formula
III to provide a substantially monodispersed mixture of activated polymers capable of
reacting with a drug; and

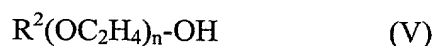
reacting the substantially monodispersed mixture of activated polymers with a
substantially monodispersed mixture of drugs under conditions sufficient to provide a
substantially monodispersed mixture of conjugates each comprising a drug coupled to an
oligomer that comprises a polyethylene glycol moiety with m+n subunits.

96. The process according to Claim 95, wherein R^2 is a fatty acid moiety or an
ester of a fatty acid moiety.

97. The process according to Claim 96, wherein the fatty acid moiety or the ester
of a fatty acid moiety comprises an alkyl moiety at least 5 carbon atoms in length.

98. The process according to Claim 95, wherein R^1 is a methyl group.

99. The process according to Claim 95, further comprising:
reacting a substantially monodispersed mixture comprising compounds having the
structure of Formula V:



with a methanesulfonyl halide under conditions sufficient to provide a substantially
monodispersed mixture comprising compounds having the structure of Formula II:

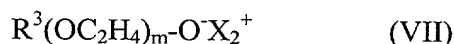


100. The process according to Claim 95, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula VI:



wherein R^2 is a lipophilic moiety;
with a substantially monodispersed mixture comprising compounds having the structure of Formula VII:



wherein R^3 is benzyl, trityl, or THP; and X_2^+ is a positive ion;

under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula VIII:

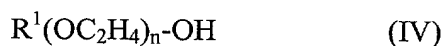


reacting the substantially monodispersed mixture comprising compounds having the structure of Formula VIII under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula V:

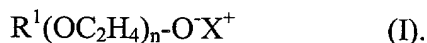


101. The process according to Claim 95, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula IV:



under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula I:



102. The process according to Claim 95, wherein the activating of the substantially monodispersed mixture comprises reacting the substantially monodispersed mixture of polymers of Formula III with N-hydroxy succinimide to provide an activated polymer capable of reacting with a drug.

103. The process according to Claim 95, wherein the drug is a polypeptide, and wherein the reacting of the substantially monodispersed mixture of activated polymers with a substantially monodispersed mixture of polypeptides comprises:

- reacting the substantially monodispersed mixture of activated polymers with one or
- 5 more amino functionalities of the polypeptide to provide a substantially monodispersed mixture of conjugates each comprising the polypeptide coupled to an oligomer that comprises a polyethylene glycol moiety with $m+n$ subunits.